Entrainment of linear and non-linear system under noise

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Theoretical models that describe oscillations in biological systems are often either a *limit cycle oscillator*, where the deterministic nonlinear dynamics gives sustained periodic oscillations, or a *noise-induced oscillator*, where a fixed point is linearly stable with complex eigenvalues and addition of noise gives oscillations around the fixed point with fluctuating amplitude. We investigate how each class of model behaves under the external periodic forcing, taking the well-studied van der Pol equation as an example. We find that, when the forcing is additive, the noise-induced oscillator can show only one-to-one entrainment to the external frequency, in contrast to the limit cycle oscillator which is known to entrain to any ratio. When the external forcing is multiplicative, on the other hand, the noise-induced oscillator can show entrainment to a few ratios other than one-to-one, while the limit cycle oscillator shows entrain to any ratio. The noise blurs the entrainment in general.

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I. INTRODUCTION

Biological systems present us with a bewildering fauna of oscillators: cell cycles[1], circadian rhythms[2–5], calcium oscillations[6], pace maker cells[7], protein responses[8–14], and so on. Sometimes, however, it is hard to see what are the minimal models behind these oscillations. Typically, the models are categorized into two classes: (i) *Limit cycle oscillator*: The fixed point is linearly unstable and the oscillations are described by stable limit cycles sustained by nonlinearity of the system in the deterministic case[11,12]. Noise (e.g. molecular noise due to limited number of copy numbers) can be added on the top of the deterministic oscillations. (ii) *Noise-induced oscillator*: The fixed point is linearly stable for the system without noise and the system relaxes to the fixed point with damped oscillations when temporally perturbed. Addition of noise to such a system is known to show sustained oscillations with fluctuating amplitude[13,14]. For some systems, both limit cycle oscillators (i) and noise-induced oscillators (ii) are proposed as a mechanism for the oscillation[11–13]. Here, we propose a way to distinguish the two, by using the phenomenon of *entrainment* to an periodic perturbation.

It is well known that, when an periodic perturbation is added to a deterministic limit cycle, the system's oscillation frequency ω will be entrained to the external frequency Ω with various rational numbers of frequencies $\omega/\Omega = P/Q$ for *all* positive integers P and Q in a *finite window of the external frequency* Ω, where the width of the window depends on the amplitude of the external forcing[15,16]. Entrainment, also called mode-locking, has been observed in variety of physical systems during the last decades, from onset of turbulence[17], Josephson junctions[18,19], one-dimensional conductors[20], semiconductors[21,22] and crystals[23]. It has been predicted, and verified experimentally, that the mode-locking structure possesses certain universal properties[15,16]. In biological systems, entrainment has been investigated theoretically for circadian rhythms[4,5] as well as in model systems for protein responses[25]. Experimental observation of entrainment in biological systems is often rather difficult due to noisy signals, but it has been observed for circadian rhythms[2,3] and synthetic genetic oscillators[24].

In this paper, we study the difference in the entrainment behavior for the limit cycle oscillators and noise-induced oscillators, taking the famous van der Pol equation with noise as an example. Especially we show that, when the external forcing is additive, the noise-

induced oscillator can entrain only at one-to-one ratio, meaning that the entrainment to other than one-to-one ratio is the sign of the dominance of the limit cycle mechanism.

II. MODEL

A. van der Pol equation

Consider the following two-dimensional equation with noise:

$$\dot{\boldsymbol{x}} = \boldsymbol{F}(\boldsymbol{x}) + \sigma^2 \boldsymbol{\Gamma}, \tag{1}$$

with

$$\boldsymbol{x} = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix}, \quad \boldsymbol{\Gamma} = \begin{pmatrix} \Gamma_1(t) \\ \Gamma_2(t) \end{pmatrix}, \tag{2}$$

$$\boldsymbol{F}(\boldsymbol{x}) = \begin{pmatrix} x_2(t) \\ -(Bx_1(t)^2 - d)x_2(t) - x_1(t) \end{pmatrix}. \tag{3}$$

Here, d, σ, and B are parameters, and $\Gamma_i(t)$ are uncorrelated, statistically independent Gaussian white noise, satisfying

$$\langle \Gamma_j(t) \rangle = 0, \quad \langle \Gamma_j(t)\Gamma_k(t') \rangle = \delta_{j,k}\delta(t - t'). \tag{4}$$

First let us consider the deterministic case, $\sigma = 0$. The model has a fixed point at $(x_1, x_2) = (0, 0)$, and the eigenvalues around this fixed point are

$$\lambda_\pm = \frac{1}{2}\left(d \pm \sqrt{d^2 - 4}\right), \tag{5}$$

indicating that the system experiences a Hopf bifurcation at $d = 0$. When $d < 0$, the fixed point relaxes to the fixed point with damped oscillation with the angular frequency $\omega_\ell(d) = \sqrt{|d^2 - 4|}/2$, while when $d > 0$ and $B > 0$ the model shows a stable limit cycle (van der Pol oscillator).

In the stochastic case with $\sigma > 0$, however, the system shows a sustained oscillation even in the linearly stable case, $d < 0$, because the noise keeps activating the oscillation with frequency ω_ℓ. This is the case of the linear p53 model introduced in Ref.[13]. When $d > 0$, $\sigma > 0$ adds fluctuations on top of the stable oscillation around the limit cycle.

B. Setup

We investigate the entrainment behavior of the model, focusing on the following three classes of parameter sets.

1. The *limit cycle oscillator*, with $d > 0$ and $B > 0$.

2. For the *noise-induced oscillator*, we consider the two subcategories.

   (a) The *linear system with a stable fixed point*, with $d < 0$ and $B = 0$, i.e., the equations are linear in $\boldsymbol{x}$ and the fixed point is stable.

   (b) The *nonlinear system with a stable fixed point*, with $d < 0$ and $B > 0$, i.e., the fixed point is linearly stable but the equations possess a nonlinear term.

When noise-induced oscillators are studied, normally only linear terms are considered. However, in reality, there are often nonlinear terms, which can play a role when distance from the stable fixed point $|\boldsymbol{x}|$ is sufficiently large. This is the reason why we consider both linear and nonlinear noise-induced oscillators.

Figure 1 shows the typical behavior of the model in each categories. The parameters are chosen so that the period and amplitude are in similar range. Without noise, the limit cycle is the only case with stable oscillation (Fig. 1a), while linear and nonlinear systems with a stable fixed point exhibit damped oscillations relaxing to the fixed point (Fig. 1bc). When noise is added, the oscillation is perturbed for limit cycle oscillator (Fig. 1d); here the noise level is chosen so that the base oscillation is still recognizable. For linear and nonlinear noise-induced oscillators (Fig. 1ef), we observe oscillations with the expected angular frequency ($\omega_\ell(-0.1) \approx 1$). In order to demonstrate the difference between the two, we apply the exact same sequence of noises in both cases. We observe a bigger difference when linear noise-induced oscillator have large ($|\boldsymbol{x}| \approx 1$) amplitude, because the nonlinear term becomes more important. Naturally this effect depends on the value of B (data not shown).

We study these oscillators under the following two kinds of external periodic perturbation.

a. Additive forcing. The first case is an *additive* forcing, in the form of

$$\dot{\boldsymbol{x}} = \boldsymbol{F}(\boldsymbol{x}) + \sigma^2 \boldsymbol{\Gamma} + \boldsymbol{A}(t), \tag{6}$$

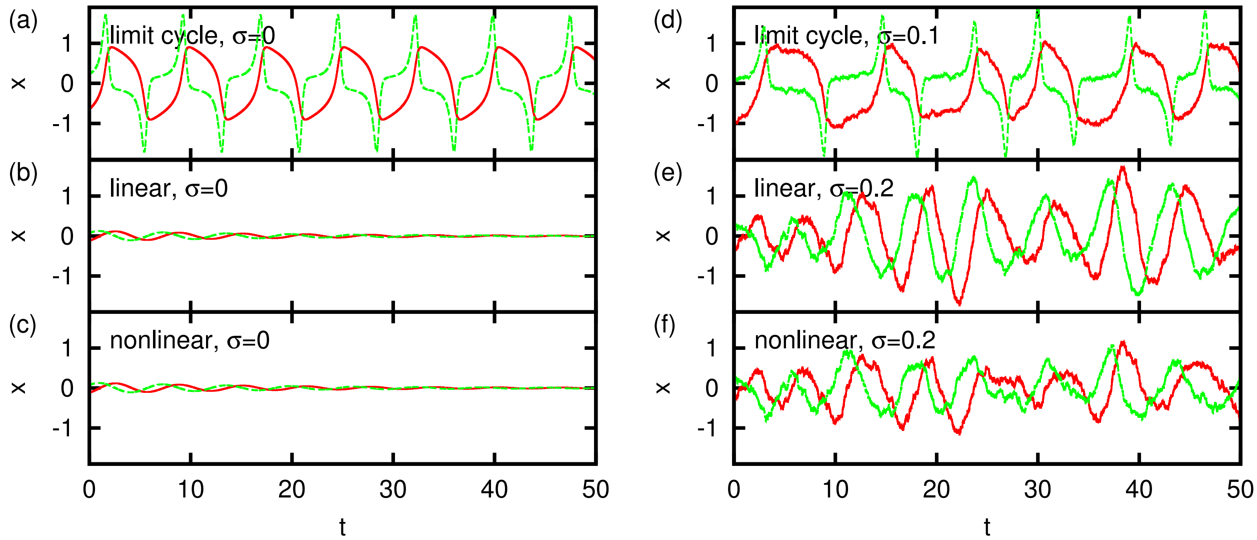

FIG. 1. (color online) The time evolution of x_1 (solid line) and x_2 (dashed line) when there is no external forcing. (a) limit cycle oscillator with $d = 2$ and $B = 10$ without noise ($\sigma = 0$). (b) linear system with $d = -0.1$ and $B = 0$ without noise ($\sigma = 0$). (c) nonlinear system with $d = -0.1$ and $B = 1$ without noise ($\sigma = 0$). For (b) and (c), the initial condition is perturbed from the fixed point to demonstrate the dumped oscillation. (d) limit cycle oscillator with $d = 2$ and $B = 10$ with noise ($\sigma = 0.1$). (b) linear system with $d = -0.1$ and $B = 0$ with noise ($\sigma = 0.2$). (c) nonlinear system with $d = -0.1$ and $B = 1$ with noise ($\sigma = 0.2$).

with

$$\boldsymbol{A}(t) = \begin{pmatrix} 0 \\ A \end{pmatrix} \cos \Omega t, \tag{7}$$

b. Multiplicative forcing. The second case is an *multiplicative* forcing (also called parametric forcing), in the form of

$$\dot{\boldsymbol{x}} = \boldsymbol{F}(\boldsymbol{x}) + \sigma^2 \boldsymbol{\Gamma} + \mathbf{M}(t)\boldsymbol{x}, \tag{8}$$

where

$$\mathbf{M}(t) = \begin{pmatrix} 0 & 0 \\ M & 0 \end{pmatrix} \cos \Omega t. \tag{9}$$

In the next section, we first present the behavior of the model under the additive forcing, and then show the parallel results for the multiplicative forcing.

III. RESULTS

A. Additive forcing

1. *Linear case without noise*

In the deterministic case with a linearly stable fixed point, the long-time behavior of the linearized equations around the fixed point under the external forcing can be analytically evaluated for any dimension as described in the following.

In the case of the additive periodic forcing, we have in general

$$\dot{\boldsymbol{x}}(t) = \mathbf{L}\boldsymbol{x}(t) + \boldsymbol{A}(t), \tag{10}$$

where $\mathbf{L}$ is a coefficient matrix of the linearized equation, and $\boldsymbol{A}(t)$ is periodic function in time with a period T, satisfying $\boldsymbol{A}(t+T) = \boldsymbol{A}(t)$.

The eigenvectors $\boldsymbol{u}_j$ of the matrix L are given by $\mathbf{L}\boldsymbol{u}_j = \lambda_j \boldsymbol{u}_j$. Since the fixed point $\boldsymbol{x} = 0$ is stable, λ_j is a complex number with the negative real part. For simplicity, we assume that there is no degeneracy of the eigenvalues and hence the $\boldsymbol{u}_j$'s form a complete set. Without loss of generality, we can expand the solution using $\boldsymbol{u}_j$ as $\boldsymbol{x}(t) = \sum_{j=1}^{d} C_j(t)\boldsymbol{u}_j$, and rewrite the equation (10) to be

$$\dot{C}_j(t) = \lambda_j C_j(t) + A_j(t) \tag{11}$$

with $A_j(t) = \boldsymbol{v}_j^t \cdot \boldsymbol{A}(t)$. Here, $\boldsymbol{v}_j^t$ is the conjugate vector of $\boldsymbol{u}_j$ in the sense that $\boldsymbol{v}_j^t \mathbf{L} = \lambda_j \boldsymbol{v}_j^t$ with normalisation $\boldsymbol{v}_j^t \cdot \boldsymbol{u}_k^t = \delta_{j,k}$.

Noting that $A_j(t+T) = A_j(t)$, we can Fourier expand the function $A_j(t)$ as

$$A_j(t) = \sum_{n=-\infty}^{\infty} F_n e^{in\frac{2\pi}{T}t}, \tag{12}$$

with n being an integer. This gives the solution to the differential equation (11) as

$$C_j(t) = C_0 e^{\lambda_j t} + \sum_{n=-\infty}^{\infty} \frac{F_n}{in\frac{2\pi}{T} - \lambda_j} \left[e^{in\frac{2\pi}{T}t} - e^{\lambda_j t} \right], \tag{13}$$

with a constant C_0.

In the long-time limit we get

$$\lim_{t\to\infty} C_j(t) = \sum_{n=-\infty}^{\infty} \frac{F_n}{in\frac{2\pi}{T} - \lambda_j} e^{in\frac{2\pi}{T}t}. \tag{14}$$

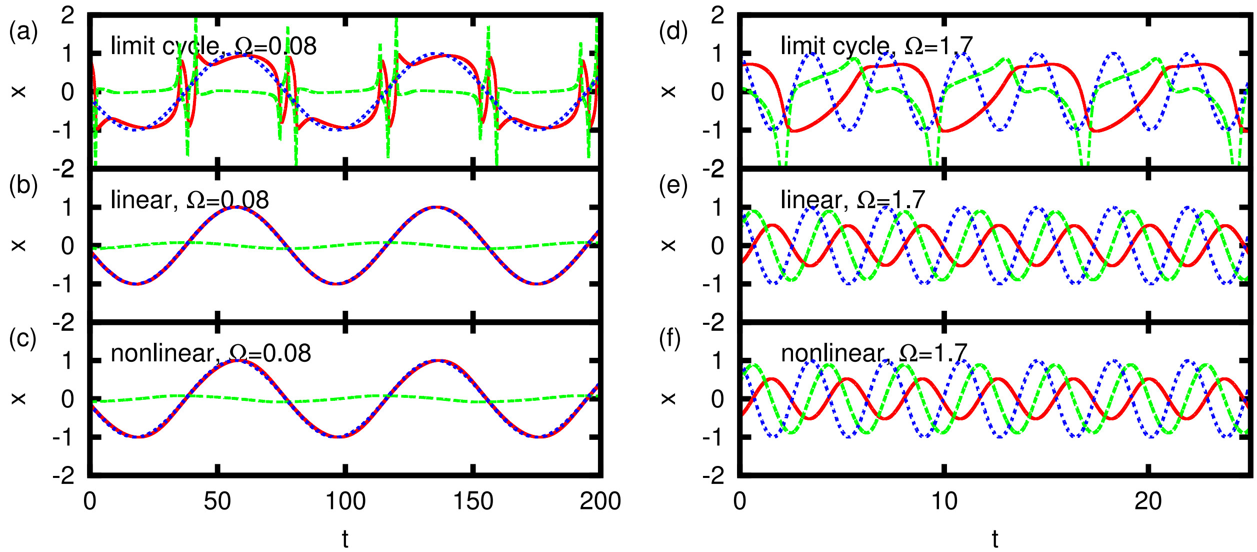

FIG. 2. (color online) The time evolution of x_1 (solid line) and x_2 (dashed line) when there is additive external forcing (dotted line, $A = 1$). The external forcing has angular frequency $\Omega = 0.08$ for (a-c), and $\Omega = 1.7$ for (d-f). (a) and (d) limit cycle oscillator with $d = 2$ and $B = 10$ without noise ($\sigma = 0$). (b) and (e) linear system with a stable fixed point with $d = -0.1$ and $B = 0$ without noise ($\sigma = 0$). (c) and (f) nonlinear system with a stable fixed point with $d = -0.1$ and $B = 1$ without noise ($\sigma = 0$). For the case with a limit cycle oscillator (a, d), the system's angular frequency can entrain to the external angular Ω with various ratios, while in the linear and nonlinear systems with a stable fixed point case (b,c,e,f) the system can only entrain to one to one ratio.

because $\Re(\lambda_j) < 0$. Therefore the solution will be always a periodic function of t with the period T in the long time limit, and contains only the frequencies that the external forcing has. In other word, the system will be always in a 1/1 entrained state if the perturbation is pure sine or cosine wave.

2. Numerical results

We now investigate numerically the entrainment behaviors for all three categories. First we demonstrate the behavior without noise, and then show how the noise modify this behavior.

a. Without noise. Figure 2 illustrates typical entrainment behaviors for additive forcing when noise is absent. With a limit cycle oscillator (Fig. 2 a, d), the system's angular frequency can entrain to the external angular Ω with various ratios, while in the linear system, one-to-one entrainment occurs (Fig. 2 b, e). The nonlinear system shows very similar behavior to the linear system, where we see only one-to-one entrainment (Fig. 2 c, f).

In order to define the system's angular frequency in a simple way, we adopt the polar coordinate (r, θ) using

$$x_1(t) = r(t)\cos\theta(t), \tag{15}$$

$$x_2(t) = r(t)\sin\theta(t), \tag{16}$$

as proposed in Ref.[26]. We define $\theta(t)$ so that $(\theta(t) - \theta(0))/2\pi$ gives the winding number, i.e., how many times the orbit went around the fixed point by time t. The system's angular frequency is numerically calculated from

$$\omega = \frac{1}{T}\left[\theta(T) - \theta(0)\right] \tag{17}$$

for long enough T (typically 1000 times external forcing period). With this definition, Fig. 2(a) shows the entrainment of the ratio $\omega/\Omega = 2/1$, while Fig. 2(d) gives $\omega/\Omega = 1/2$.

b. With noise. The addition of noise blurs the entrainment behavior, as depicted in Fig. 3. For the limit cycle oscillator (Fig. 3a and d), we can see that the noise makes the orbit irregular, which can make the phase to slip. In the linear noise-induced oscillator for small external angular frequency, we can clearly see that the noise induces the oscillation with angular frequency close to ω_ℓ on top of one-to-one entrainment behavior (Fig. 3b). When Ω is larger than ω_ℓ, the external angular frequency seems to dominate. The nonlinear noise-induced oscillator behaves again very similar to the linear case in entrainment behavior (Fig. 3c and f). The visible difference is a suppression of large amplitude by the nonlinear term.

c. "Devil's staircase" and "Arnold's tongues". For deterministic limit cycles, the plot of ω/Ω vs Ω for a fixed amplitude of external forcing shows a infinitely complex structure with fractal nature, known as Devil's staircase[15,16,26]. For the present system of limit cycle oscillator without noise, this is also observed as shown in Fig. 4(a) (solid line). As noise increases, the phase slips occasionally, therefore narrow entrainment regions become harder to recognize (Fig. 4a, dashed and dotted line). For the systems with a stable fixed point,

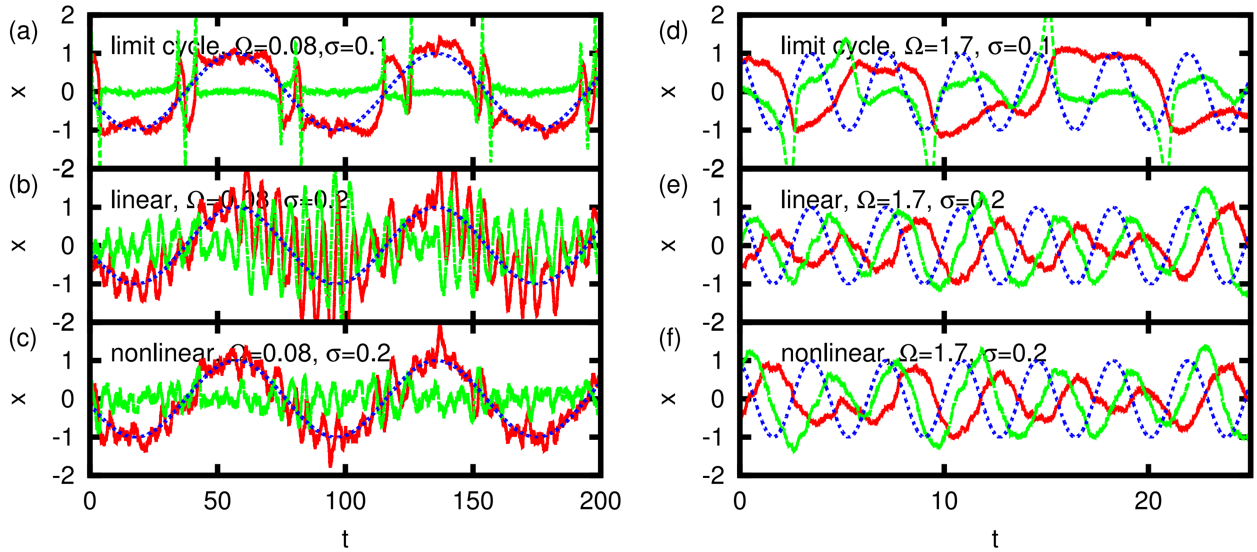

FIG. 3. (color online) The time evolution of x_1 (solid line) and x_2 (dashed line) when there is additive external forcing (dotted line, $A = 1$). The external forcing has angular frequency $\Omega = 0.08$ for (a-c), and $\Omega = 1.7$ for (d-f). (a) and (d) limit cycle oscillator with $d = 2$ and $B = 10$ with noise ($\sigma = 0.1$). (b) and (e) linear noise-induced oscillator with $d = -0.1$ and $B = 0$ with noise ($\sigma = 0.2$). (c) and (f) nonlinear noise-induced oscillator with $d = -0.1$ and $B = 1$ with noise ($\sigma = 0.2$). For the limit cycle oscillator (a and d), the noise makes the orbit irregular, and the phase sometime slips. In the linear noise-induced oscillator for small external angular frequency, we can clearly see that the noise put the oscillation with angular frequency close to ω_ℓ on top of one-to-one entrainment behavior (b). When Ω is larger than ω_ℓ (e), the external angular frequency seems to dominate. The nonlinear noise-induced oscillator behaves again very similar to the linear case in entrainment behavior (c and f), except for the suppression of large amplitude.

there is only one-to-one entrainment for the no noise case (Fig. 4b, solid line), while noise induced oscillation around the entrained solution will add some phase slips giving a change in the angular frequency when the entrainment is not so strong, resulting in an escape from the one-to-one ratio as shown in Fig. 4(b).

When entrainment regions for various values of ω/Ω are plotted in the A-Ω plain, it gives an "Arnold's tongue" structure for the deterministic limit cycles: The entrainment regions widen as the external forcing amplitude A grows, resulting in tongue-like shapes of the entrainment region – when A is large enough the tongues start to overlap[15,16]. This can be seen in the limit cycle oscillator without noise in Fig. 5 (a). When noise is added, the phase

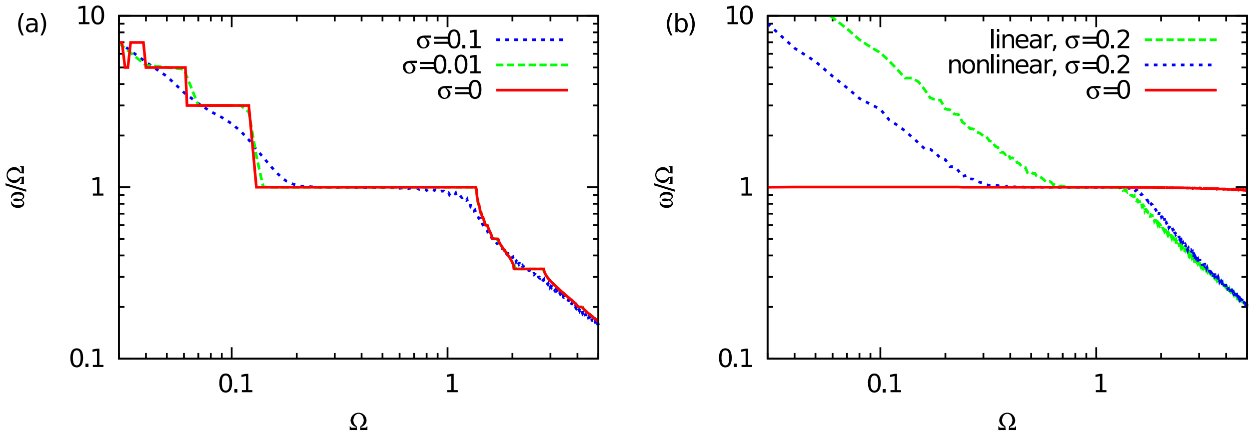

FIG. 4. "Devil's staircase" for limit cycle oscillator (a) and linear and nonlinear systems with a stable fixed point (b) under additive forcing with $A = 1$. (a) The limit cycle oscillator with $d = 2$ and $B = 10$ with $\sigma = 0.01$ (dotted line), $\sigma = 0.1$ (dashed line) and $\sigma = 0$ (solid line). (b) The systems with a stable fixed point ($d = -0.1$). For the case without noise $\sigma = 0$ (solid line), both linear ($B = 0$) and nonlinear ($B = 1$) systems show only one-to-one entrainment. With noise, the noisy oscillations around the one-to-one entrained orbit is induced, as shown with $\sigma = 0.2$ (linear case with $B = 0$ is shown by dashed line, and nonlinear case with $B = 1$ is shown by dotted line).

of the oscillator sometimes slips, resulting in narrower tongues (Fig. 5 b). For the noise-induced oscillators (i.e. with a stable fixed point), there exists only 1/1 entrainment without noise, and with noise 1/1 entrainment is the only case that gives the tongue-like structure, both for the linear and nonlinear cases (Fig. 5 cd). We see other ratios of entrainment "regions", because for a given A with changing Ω, ω/Ω changes continuously outside of the entrainment region (e.g. Fig.4 b).

B. Multiplicative forcing

1. Linear case without noise

We next consider the multiplicative forcing

$$\dot{\boldsymbol{x}}(t) = \mathbf{L}\boldsymbol{x}(t) + \mathbf{M}(t)\boldsymbol{x}(t), \tag{18}$$

where the matrix $\mathbf{M}(t)$ satisfies

$$\mathbf{M}(t + T) = \mathbf{M}(t) \tag{19}$$

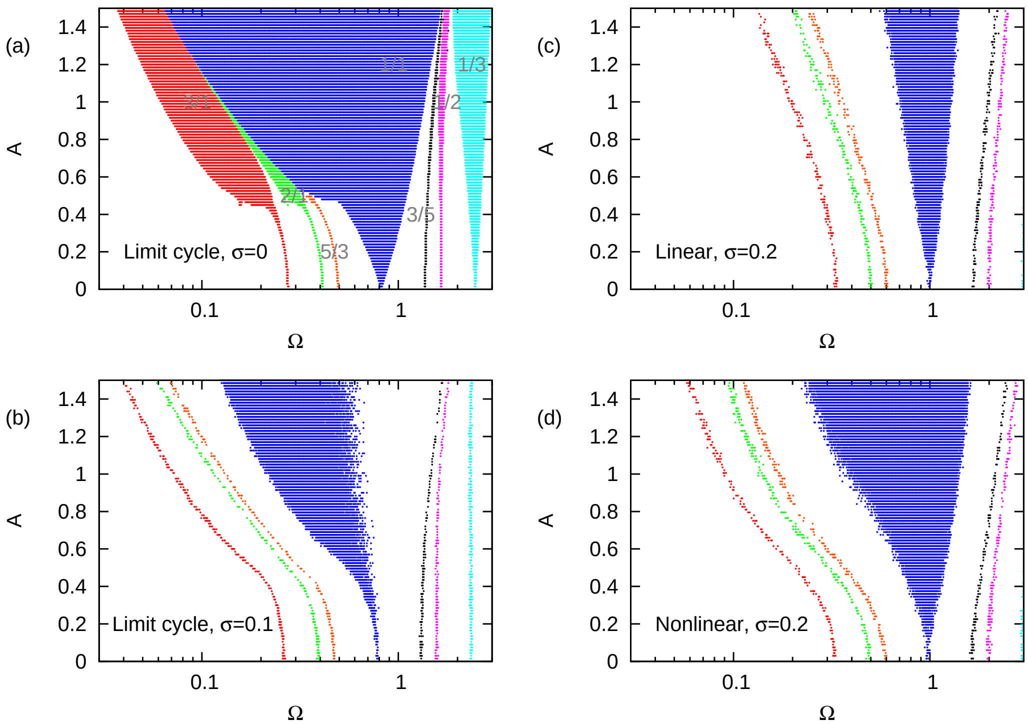

FIG. 5. "Arnold's tongue" with additive forcing for limit cycle oscillator without (a) and with (b) noise and for noise-induced oscillator with noise for linear (c) and nonlinear (d) case. The horizontal axis is the external frequency Ω, and the vertical axis is the forcing amplitude A' Entrainment is defined as ω/Ω is within 1% of the given value. (a) The limit cycle oscillator with $d = 2$ and $B = 10$ with $\sigma = 0.0$, which shows standard 'Arnold's tongue'. Noise ($\sigma = 0.1$) make phases to slip, resulting in smaller region of entrainment (b). For noise induced oscillator with noise (c: $d = -0.1, B = 0, \sigma = 0.2$, d: $d = -0.1, B = 1, \sigma = 0.2$), the tongue-like triangle structure is observed only for 1/1 entrainment.

with $T = 2\pi/\Omega$. It is known from Floquet theory[27] that the solution matrix of this equation is expressed as

$$\mathbf{Q}(t) = e^{\mathbf{\Lambda} t}\mathbf{U}(t), \tag{20}$$

where

$$\mathbf{U}(t+T) = \mathbf{U}(t), \tag{21}$$

and a general solution is the linear combinations of column vectors consisting of $\mathbf{Q}(t)$. The eigenvalues of the matrix $\mathbf{\Lambda}$, called Floquet exponents, determine the stability of the solution: The solution will converge to the fixed point when the real parts of the Floquet exponents are all negative, and diverges if some Floquet exponent have positive real parts. Therefore, no entrainment behavior will be observed for a linear noise-induced oscillator without noise under multiplicative forcing.

In Fig.6, we show numerically calculated the maximum real part of the Floquet exponents λ_R for (18) with (9) with $d = -0.1$ and $B = 0$, as a function of amplitude of forcing M and external freqency Ω. When $\lambda_R < 0$ (dark blue region), $|\boldsymbol{x}|$ will exponentially decays to zero, otherwise $|\boldsymbol{x}|$ will diverge except for the marginal case $\lambda_R = 0$.

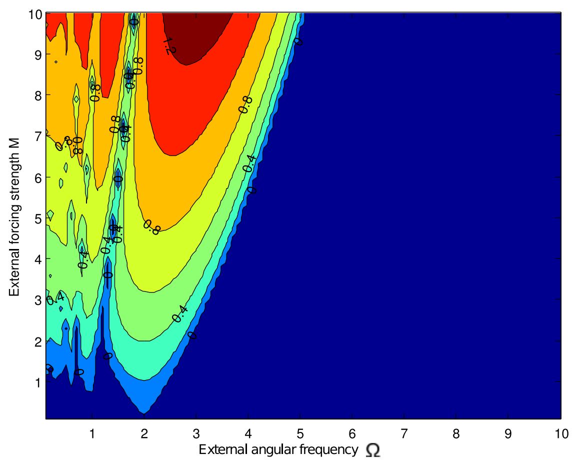

FIG. 6. Maximum real part of the Floquet exponent λ_R for various M and Ω, for the linear system with stable fixed point ($d = -0.1$ and $B = 0$) without noise ($\sigma = 0$).

2. Numerical results

a. Without noise. Figure 7 shows the entrainment behaviors for multiplicative forcing. For the limit cycle oscillator (Fig. 7 ac), there is no qualitative difference from the additive noise case, i.e., the system shows entrainment with various frequency ratio $\omega/\Omega = P/Q$. For the linear system with a stable fixed point without noise, on the other hand, the system can either decay to the fixed point (Fig. 7 b) or diverge (Fig. 7 d), which can be predicted from the Flouquet exponents (Fig.6). When nonlinear term is added, it does not prevent the decay (Fig. 7 c), but the divergent behavior is suppressed and system shows the entrainment

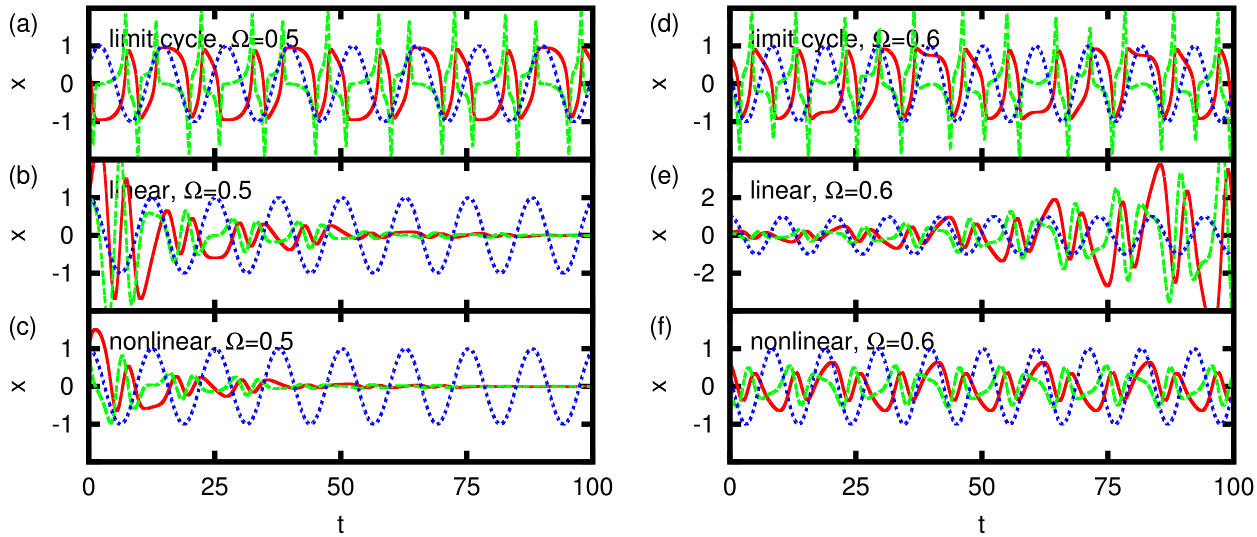

FIG. 7. (color online) Without noise: The time evolution of x_1 (solid line) and x_2 (dashed line) when there is multiplicative external forcing (dotted line, $M = 1$). The external forcing has angular frequency $\Omega = 0.5$ for (a-c), and $\Omega = 0.6$ for (d-f). (a) and (d) limit cycle oscillator with $d = 2$ and $B = 10$ without noise ($\sigma = 0$). (b) and (e) linear system with a stable fixed point with $d = -0.1$ and $B = 0$ without noise ($\sigma = 0$). The transient behavior is shown. Note that the y-range in (e) is different from other plots. (c) and (f) nonlinear system with a stable fixed point with $d = -0.1$ and $B = 1$ without noise ($\sigma = 0$). The limit cycle ocsillator shows entrainments (a,d), but the linear system either decays to zero (b) or diverges (e). The nonlinear system either decays (c) or entraines (f).

behavior (Fig. 7 f). The frequency ratio ω/Ω is not necessarily 1/1; the example in Fig. 7(f) gives $\omega/\Omega = 3/2$.

b. With noise. When noise is added, the behavior changes drastically in the noise-induced oscillators, as shown in. Fig. 8. The noise can induce the oscillation with the angular frequency close to ω_ℓ for the case where the no-noise system would decay to the fixed point (Fig. 8 b, c). On the other hand, in the linear noise-induced oscillator, adding noise does not prevent divergence (Fig. 8 e). For the parameters where no-noise system would entrain, the noise blurs the entrainment due to occasional phase slip for both limit cycle oscillator (Fig. 8 ac) and nonlinear noise-induced oscillator (Fig. 8 f).

c. "Devil's staircase" and "Arnold's tongue". We also study the "Devil's staircase" for the multiplicative forcing. For the limit cycle oscillator without noise, we again see

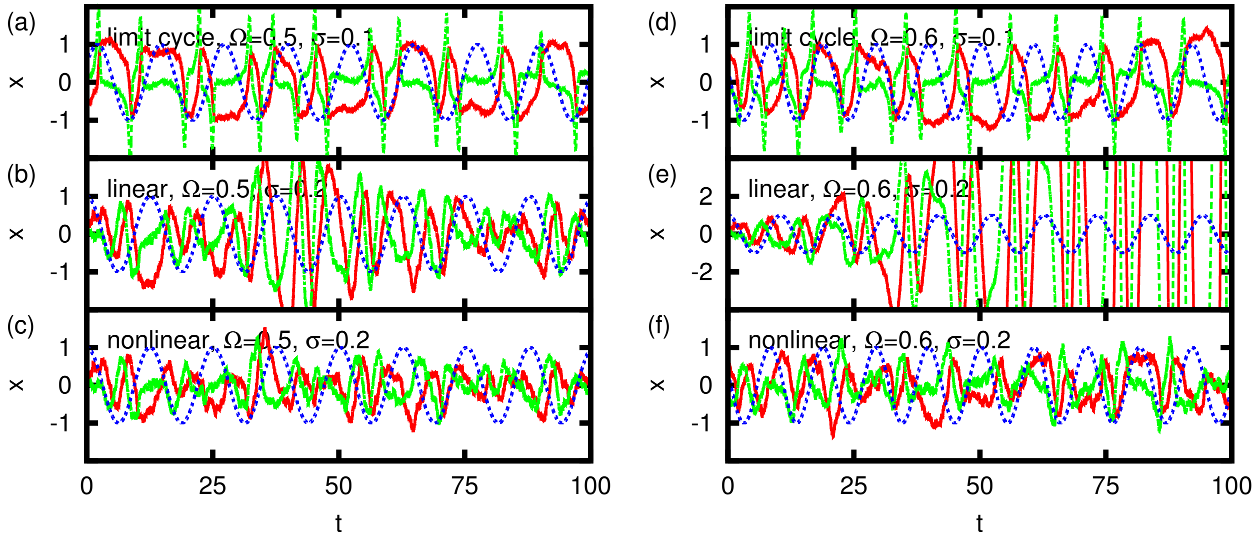

FIG. 8. (color online) With noise: The time evolution of x_1 (solid line) and x_2 (dashed line) when there is multiplicative external forcing (dotted line, $M = 1$). The external forcing has angular frequency $\Omega = 0.5$ for (a-c), and $\Omega = 0.6$ for (d-f). (a) and (d) limit cycle oscillator with $d = 2$ and $B = 10$ with noise ($\sigma = 0.1$). (b) and (e) linear noise-induced oscillator with $d = -0.1$ and $B = 0$ with noise ($\sigma = 0.2$). Note that the y-range in (e) is different from other plots. (c) and (f) nonlinear noise-induced oscillator with $d = -0.1$ and $B = 1$ with noise ($\sigma = 0.2$). The limit cycle ocsillator shows entrainments with some phase slips (a,d). For the linear and nonlinear system, the noise induces the oscillatory behavior, for the parameters where the system would decay without noise (b,c).

proper devil's staircase, where noise will blur the entrainment behaviors (Fig.9 a). For the noise-induced oscillators, only the nonlinear case is studied because the linear case may diverge depending on the parameter values. Without noise, we see discrete finite regions of entrainment (Fig.9 b squares), while noise induces the oscillations in the decaying region resulting in a continuous line (Fig.9 b dashed line).

The Arnold's tongue structure for the limit cycle is similar to those in the additive forcing case, as seen in Fig.10(a) and (b). The Arnold's tongues for all the entrainment ratios are observed without noise, and noise makes the regions smaller. For the nonlinear system with a stable fixed point without noise, there are entrainment regions for a few rational ratios, but the ones that appear are problem specific - for instance, in the present case, the $\omega/\Omega = 1/3$ is not observed at all in Fig.10(c). With noise (Fig.10d), the entrainment regions shrinks,

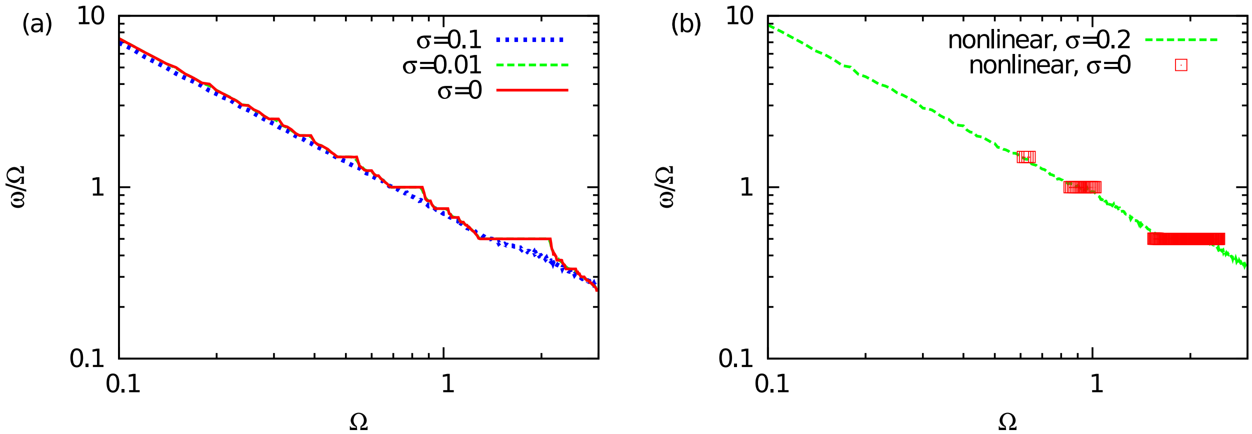

FIG. 9. "Devil's staircase" for limit cycle oscillator (a) and nonlinear noise-induced oscillator (b) under multiplicative forcing with $M = 1$. (a) The limit cycle oscillator with $d = 2$ and $B = 10$ with $\sigma = 0.01$ (dotted line), $\sigma = 0,1$ (dashed line) and $\sigma = 0$ (solid line). (b) The nonlinear system with a stable fixed point with $d = -0.1$ and $B = 1$. For the case without noise $\sigma = 0$ (solid line), the decaying region where $\boldsymbol{x}$ goes to the fixed point is not shown, resulting in three discrete entrainment region. With noise, oscillation is induced in the decaying regime also, resulting in continuous line as shown for $\sigma = 0.2$ (dashed line).

but at the same time the system can occasionally pass the given ratio of ω/Ω, resulting in narrow line of "fake" entrainment.

IV. SUMMARY AND DISCUSSION

Our motivation behind this work was to ask: Can one by applying an external periodic forcing and studying entrainment determine whether an oscillating system is driven by a linear mechanism (noise induced oscillator) or a non-linear mechanism (limit cycle oscillator)? Our answer to this question is partly yes. Our obtained results on entrainment behavior of oscillators are summarized in Table I.

When the forcing is additive, there is clear difference between the limit cycle oscillators and the noise-induced oscillators. The former can entrain to any frequency ratio, while the latter shows only one-to-one entrainment. Therefore, if one see entrainment to $P/Q \neq 1$ ratio, under additive forcing, it is a sign of limit cycle oscillator.

When the forcing is multiplicative, the non-linear noise-induced oscillators can also show

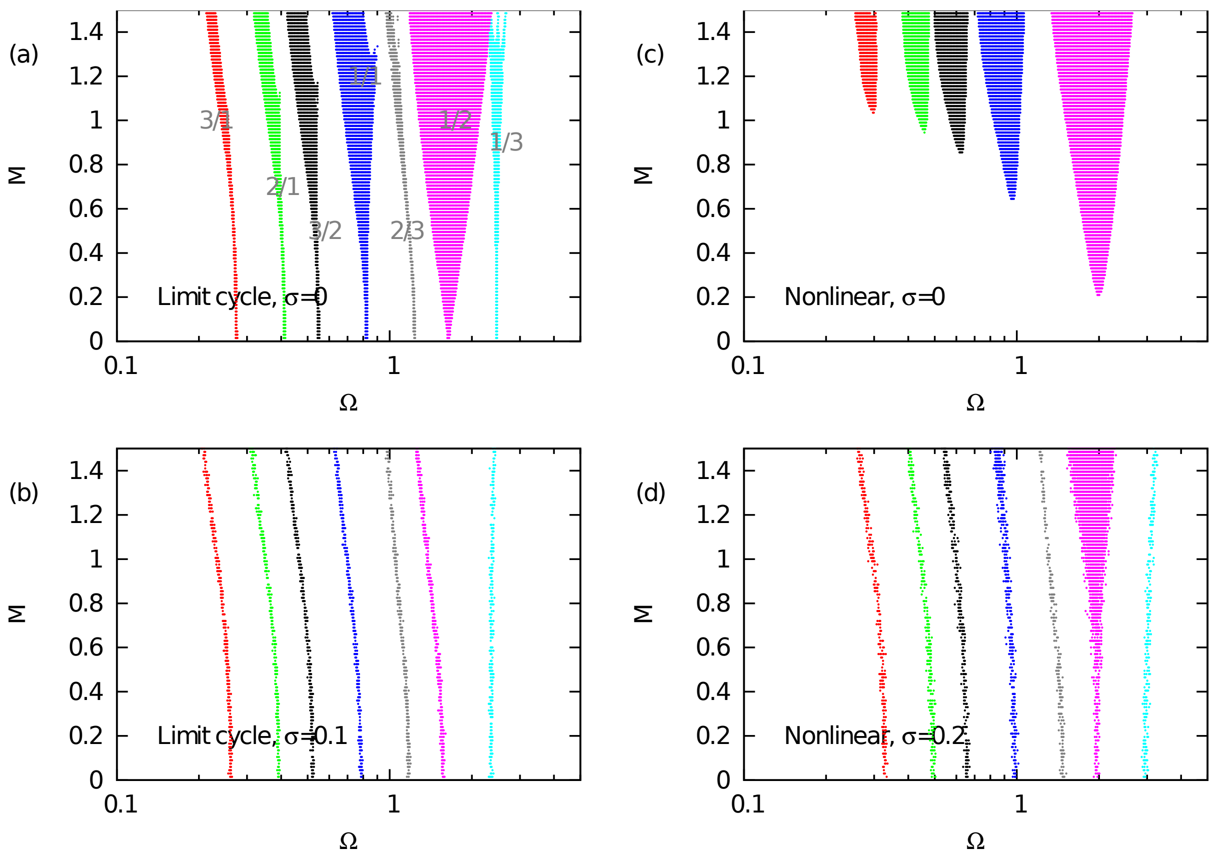

FIG. 10. "Arnold's tongue" with multiplicative forcing for limit cycle oscillator without (a) and with (b) noise and for nonlinear system with a stable fixed point without (c) and with noise (d). The horizontal axis is the external frequency Ω, and the vertical axis is the forcing amplitude M. Entrainment is defined as ω/Ω is within 1% of the given value. (a) The limit cycle oscillator with $d = 2$ and $B = 10$ with $\sigma = 0$ shows standard 'Arnold's tongue', while the noise ($\sigma = 0.1$) makes the region of entrainment smaller (b). For nonlinear noise induced oscillator ($d = -0.1, B = 1$; c), there are a few entrainment regions for no noise case ($\sigma = 0$), but not all the ratios are observed. For (c), the exponentially decaying case were excluded numerically by the following way: The equations are integrated with initial condition $x(1) = 1$ and $x(2) = 0$, and if the average amplitude for $390\pi/\Omega < t < 400\pi/\Omega$ is less than 90% of the average amplitude for $200\pi/\Omega < t < 210\pi/\Omega$, then the solution is excluded.

$P/Q \neq 1$ ratio entrainment. If the system is noise-induced oscillator and the non-linear term is small, one might be able to capture the diverging tendency of the amplitude, because saturation happens when the amplitude is large enough to make the non-linear term relevant.

TABLE I. Summary of entrainment behavior of oscillators under additive and multiplicative forcing. A and M in the "force" column represent additive and multiplicative forcing, respectively.

Oscillator	No noise	With noise	Force
Limit cycle	entrainment to any P/Q	entrainment to any P/Q with phase slips	A
	entrainment to any P/Q	entrainment to any P/Q with phase slips	M
Linear noise-induced	one-to-one entrainment*	one-to-one entrainment* with phase slips	A
	decay or diverge	noise-induced oscillation with $\sim \omega_\ell$ or diverge	M
Nonlinear noise-induced	one-to-one entrainment*	one-to-one entrainment* with phase slips	A
	small decay or some P/Q entrainment	noise-induced oscillation with $\sim \omega_\ell$ or some P/Q entrainment with phase slips	M

* All the frequencies contained in the forcing can be observed.

In such a case, one might see big difference in amplitude for a fixed M with varying Ω.

We thus urge experiment to be performed on oscillating biological systems. It is well known that some proteins (p53, NF-kB, Wnt) can oscillate in cells under stress responses. In the case of p53, both non-linear[11,12] and linear models have been proposed[13]. By applying an external time dependant signal such as DNA damaging radiation or drugs which specifically perturb the p53 circuit, it might be possible to entrain the internal oscillation and draw conclusions on the basis of our results summarized in Table I. In the case of NF-kB oscillations, one might be able to entrain the internal oscillation by an externally varying cytokine (like TNF) signal[25]. Potentially, it could lead to a way of controlling the DNA-repair pathway.

Finally, we would like to briefly comment on "noise-induced" oscillations by mechanisms other than the linear model studied here. It has been long known that, when noise is added to excitable system with a stable fixed point, regular oscillatory behaviour can be observed at a certain level of noise (coherence resonance)[28,29]. Since nonlinearity plays an important role in oscillation, such a system shows mode-locking behaviour similar to the deterministic nonlinear oscillators[30]. More recently, in gene network models with negative feedback, it has been shown that the noise due to finiteness of the number of molecules can modify the condition for oscillatory behaviour[31] or enhance the oscillation[32]. It would also be interesting

to see the entrainment behaviour in such systems.

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